Adverse events of MVAC chemotherapy in patients with advanced urothelial cancer of the bladder

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ADVERSE EVENTS OF MVAC CHEMOTHERAPY IN PATIENTS WITH ADVANCED UROTHELIAL CANCER OF THE BLADDER

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There have only been a few reports about adverse events of methotrexate, vinblastine, adriamycin and cisplatin (MVAC) chemotherapy under supportive care with granulocyte stimulating factor (G-CSF) and 5-hydroxytryptamine 3 receptor (5-HT_3R) antagonists. The purpose of this study was to retrospectively review the adverse events of the chemotherapy.

We analyzed 59 patients with advanced bladder cancer who received MVAC chemotherapy at Sapporo Medical University hospital from January 1992 to September 2004. The adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 (Japanese edition).

Thirty-one of the 59 patients (52.6%) received MVAC in the neoadjuvant setting. Two courses of chemotherapy were most frequently used in the neoadjuvant and adjuvant settings, and treatment of metastatic or recurrent lesions. More than 90% of patients experienced hematological adverse events such as some grade of leukocytopenia and neutropenia in each course of the chemotherapy. Grade 3 or 4 neutropenia was seen in 60–75% of patients. Grade 3 or 4 leukopenia and/or neutropenia in the first course of the chemotherapy was associated with patients with impaired renal function (60 mL/min$\leq$ creatinine clearance $<$80 mL/min). Febrile neutropenia was found in 6 patients (5.0%), including one who died of subsequent septic shock and adult respiratory distress syndrome. Nausea was seen in 70–80% of patients.

MVAC chemotherapy for advanced bladder cancer was performed with tolerable adverse events. The current results provide relevant information mainly for those who need 2 courses of chemotherapy in the neoadjuvant or adjuvant setting.

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Key words : MVAC chemotherapy, Advanced bladder cancer, Adverse events, Supportive care

INTRODUCTION

Combination chemotherapy using methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) has been used as the standard regimen for treatment of metastatic or locally advanced urothelial carcinoma since Stenberg et al.[1] reported its efficacy in 1985. However, several studies pointed out that the chemotherapy eventually produced severe adverse events, including treatment-related death in some patients[2–5]. Tannock et al.[5] suggested that MVAC chemotherapy should not be used in an adjuvant or neoadjuvant setting except in the context of a clinical trial because of the severe toxicity of this regimen. However, a recent randomized control trial by the South Western Oncology Group (SWOG) showed that 3 courses of neoadjuvant MVAC before radical cystectomy were safely performed with acceptable rates of adverse events[6]. Furthermore, the SWOG study revealed that neoadjuvant MVAC followed by radical surgery improved survival of patients with locally advanced bladder cancer compared to those with surgery alone. A recent meta-analysis indicated that survival of patients with invasive bladder cancer was improved by cisplatin-based neoadjuvant chemotherapy[7,8]. Thus, MVAC may be performed more often for patients with invasive bladder cancer. Unfortunately there are only a few reports about adverse events with this chemotherapy, in particular those after the time when the supportive drugs such as granulocyte colony-stimulating factor (G-CSF) and 5-hydroxytryptamine 3 receptor (5-HT_3R) antagonists were routinely used[2–4,6].

In this study we reviewed our own experience with MVAC with emphasis on the results of adverse events.

PATIENTS AND METHODS

Patients

We retrospectively analyzed 59 patients with invasive or metastatic urothelial carcinoma of the bladder who received MVAC chemotherapy at Sapporo Medical University hospital from January 1992 to September 2004. Patients who received MVAC before December 1991 were excluded because G-CSF and 5-HT_3 R antagonists, which were used to reduce the severity of hematological and gastrointestinal toxicities, respectively, were not available for routine use. All patients had histologically proven urothelial carcinoma of the bladder. Patients were required to have a performance

status of 0–2, an adequate bone marrow reserve (WBC count $\geq$3,000/mm^3, platelets $\geq$100,000/mm^3, and hemoglobin $\geq$8.0 g/dL), renal function (creatinine clearance $\geq$60 mL/min) and hepatic function. Patients who had a past history of systemic chemotherapy, radiation therapy or immunotherapy were not included in the study.

MVAC chemotherapy and supportive care

The chemotherapy was performed according to the schedule described by Stenberg et al.[1] as follows: methotrexate (30 mg/m^2) on days 1, 15 and 22; vinblastine (3 mg/m^2) on days 2, 15 and 22; and doxorubicin (30 mg/m^2) and cisplatin (70 mg/m^2) on day 2. This schedule was designated as one course of chemotherapy. Patients received methotrexate and vinblastine on days 15 and 22 if the neutrophil count exceeded 1,000/mm^3 and the platelets exceeded 100,000/mm^3. Dose modification according to the creatinine clearance was not applied in any of the 59 patients, and MVAC chemotherapy was not performed in patients with severely impaired renal function (creatinine clearance $<$60 ml/min).

We used G-CSF when the neutrophil count was less than 500/mm^3 or less than 1,000/mm^3 with fever of 38.5°C or higher and discontinued it when neutrophils reached 5,000/mm^3 or more. If the patient had febrile neutropenia (neutrophils $<$1,000/mm^3 and a fever of 38.5°C or higher), antibiotics were administered. Prophylactic use of 5-HT$_3$R antagonists was done before the administration of cisplatin on day 2. Corticosteroids were not routinely used for patients in this study.

We evaluated adverse events according to the Common Terminology Criteria for Adverse Events version 3.0 (Japanese edition)[6]. Liver and renal dysfunctions were assessed mainly by the levels of serum aspirate aminotransferase (AST) and alamine aminotransferase (ALT), and serum creatinine, respectively, during chemotherapy. The worst adverse event during treatment was regarded as the event.

We evaluated the adverse events of first to third course in this study. We assessed the factors which may associate with the occurrence of grade 3 or greater leukocytopenia and/or neutropenia. Age and renal function (creatinine clearance) were divided into subgroups by each median. Statistical analysis was calculated using logistic regression analysis. Comparison of the toxicities of the courses was done with the Student t test. A p-value of $<$0.05 was considered statistically significant.

RESULTS

Patients' Characteristics

Table 1 shows the characteristics of the 59 patients in this study. The median age was 62 years (range 37–75). Thirty-one (52.6%) of the 59 patients received MVAC in the neoadjuvant setting. Two courses of chemotherapy were most frequently used in each setting.

Table 1. Patients' demographics and clinical characteristics

Total number of patients	59	
Median age of patients (range)	62	(37–75)
Sex		
Male (%)	49	(83.1)
Female (%)	10	(16.9)
Chemotherapy setting and number of courses of chemotherapy		
Neoadjuvant (%)	31	(52.6)
1 course (%)	0	(0)
2 courses (%)	28	(47.5)
3 or more courses (%)	3	(5.1)
Adjuvant (%)	12	(20.3)
1 course (%)	2	(3.4)
2 courses (%)	8	(13.6)
3 or more courses (%)	2	(3.4)
Metastasis or recurrence (%)	16	(27.1)
1 course (%)	4	(6.8)
2 courses (%)	7	(11.9)
3 or more courses (%)	5	(8.5)
Performance status		
0 (%)	53	(89.8)
1 (%)	6	(10.2)

Two patients received MVAC chemotherapy for both the neoadjuvant and adjuvant setting. Only adverse events in the neoadjuvant chemotherapy were assessed in these patients.

Cancellation of scheduled chemotherapy

Of the 59 patients who were scheduled to receive the second course of MVAC, the chemotherapy was cancelled for 6 (10.2%), consisting of 2 with renal dysfunction, 2 with severe nausea and 2 with sepsis, all of which occurred in the first course. Similarly, the third course was cancelled for 3 of the 13 patients (23.1%) who were scheduled to receive chemotherapy. Since the nadir of the neutrophil level in the first course of chemotherapy usually occurred at days 13–17, which will be discussed in detail below, about 40% of patients in each course were not able to receive the day 15 chemotherapy (Table 2). In the first and second courses of chemotherapy, the day 22 chemotherapy was cancelled for more than 20% of patients. Thus, less than half of the patients completed the chemotherapy on days 15 and 22. The reason for skipping the day 15 and/or 22 chemotherapy was grade 3 or 4 leukopenia/neutropenia in all patients.

Adverse hematological events

Leukocytopenia and neutropenia were the most frequent adverse events (Table 3). More than 90% of patients experienced some grade of leukocytopenia and neutropenia in each course of chemotherapy. Grade 3 or 4 neutropenia was seen in 60–75% of patients. Second or third course of the chemotherapy did not

Table 2. Completion of the chemotherapy on days 15 and 22 in each course

Chemo. X course	No. of pts.	Completion of Chemo. X (%)			
		Yes for days 15 and 22	Yes for day 15 but no for day 22	No for day 15 and yes for day 22	No for days 15 and 22
1	59	44.1	8.5	27.1	16.9
2	52	50.0	13.5	28.8	9.6
3	10	50.0	10.0	30.0	10.0

Chemo. X : chemotherapy. No of pts. : number of patients. Yes : completion of day 15 or 22 chemotherapy. No : cancellation of day 15 or 22 chemotherapy.

Table 3. Adverse hematological events

Toxicity	Courses of Chemo. X	No. of pts.	Grade (%)				
			1	2	3	4	5
Leukocytopenia	1	58	20.3	33.9	28.8	6.8	0
	2	52	21.2	38.5	17.3	5.8	0
	3	10	10.0	50.0	20.0	10.0	0
Neutropenia	1	53	5.1	6.8	37.3	37.3	0
	2	48	11.5	15.4	36.5	25.0	0
	3	9	0	30.0	40.0	20.0	0
Thrombocytopenia	1	59	22.0	6.8	11.9	0	0
	2	52	30.8	7.7	9.6	0	0
	3	10	20.0	30.0	10.0	0	0
Anemia	1	59	30.5	27.1	3.4	1.7	0
	2	52	25.0	42.3	19.2	0	0
	3	10	20.0	80.0	0	0	0
Febrile neutropenia	1	59			5.1	0	1.7
	2	52			3.8	0	0
	3	10			0	0	0

Chemo. X : chemotherapy. No. of pts. : number of patients.

necessarily increase the frequency and grade of leukocytopenia or neutropenia. Six episodes of febrile neutropenia were found in 6 patients. Although 5 of these patients were successfully treated without development of serious events, a 74-year-old man with metastatic disease developed septic shock and died of respiratory insufficiency in the first course of chemotherapy. Severe thrombocytopenia was less frequent and no one required transfusion of platelets. Grade 3 anemia was more frequently found in the second course than in the first. Two patients (3.4%) in the first course and 4 (7.7%) in the second required the transfusion of red blood cells. There were no other adverse events related to blood/bone marrow functions.

We assessed factors that may associate with the development of grade 3 or greater leukocytopenia and/or neutropenia in each course of chemotherapy (Table 4). Univariate logistic regression analyses of clinical and demographic characteristics revealed that the frequency of grade 3 or 4 leukopenia and/or neutropenia in the first course of the chemotherapy was significantly higher in patients with impaired renal function (<80 mL/min) ($p=0.04$). The occurrence of grade 3 or 4 leukocytopenia and/or neutropenia in the second course had significant association with that in the first course ($p=0.03$).

Adverse non-hematological events

Table 5 shows adverse non-hematological events other than loss of hair. Nausea was the most frequently occurring event in the study during chemotherapy. Although it was not significant, the grade and frequency of nausea tended to decrease as the number of courses increased. Vomiting was seen in 39% of patients in the first course of chemotherapy with a gradual decrease in its frequency in the second and third courses. Grade 3 or more severe mucositis and diarrhea were rare in our study.

Most of the liver dysfunctions found in 20% of patients were mild and did not require specific treatment. However, one patient experienced grade 3 adverse events that were probably caused by methotrexate. The patient was successfully treated with specific drug therapy without permanent liver dysfunction and VAC chemotherapy without methotrexate was safely performed without liver dysfunction in the second course. There were no patients who had findings of liver dysfunction without abnormal elevation of AST or ALT.

Table 4. Univariate analysis of factors associated with leukocytopenia and/or neutropenia of grade 3 or greater in each course of chemotherapy

Factors to be studied	Subgroups			Chemotherapy	
				First course#	Second course##
Age	≥65 y.o. (n=26)# (n=24)##	vs.	<65 y.o. (n=33)# (n=28)##	p=0.15	p=0.41
Performance status	0 (n=53)# (n=47)##	vs.	1 (n=6)# (n=5)##	p=0.97	p=0.97
Sex	Male (n=48)# (n=45)##	vs.	Female (n=11)# (n=5)##	p=0.88	p=0.27
Chemotherapy setting	Neoadjuvant (n=31)# (n=30)##	vs.	Adjuvant (n=12)# (n=10)##	p=0.84	p=0.16
Metastasis	No (n=43)# (n=42)##	vs.	Yes (n=16)# (n=10)##	p=0.59	p=0.17
Renal function (Ccr)	<80 mL/min (n=32)# (n=14)##	vs.	≥80 mL/min (n=27)# (n=17)##	p=0.04	p=0.09
Grade 3 or greater leukocytopenia and/or neutropenia in the first course	No (n=7)##	vs.	Yes (n=45)##		p=0.03
Leukocyte count before chemotherapy	(n=59)# (n=52)##			p=0.37	p=0.88

Table 5. Adverse non-hematological events

Toxicity	Courses of Chemo. X	Grade (%)				
		1	2	3	4	5
Malaise	1	64.4	1.7	1.7	0	0
	2	59.6	1.9	0	0	0
	3	60.0	10.0	0	0	0
Nausea	1	42.4	15.3	20.3	0	0
	2	32.7	28.8	15.4	0	0
	3	20.0	40.0	10.0	0	0
Vomiting	1	28.8	6.8	3.4	0	0
	2	17.3	3.8	1.9	0	0
	3	10.0	0	0	0	0
Mucositis	1	10.2	1.7	0	0	0
	2	11.5	1.9	0	0	0
	3	10.0	0	0	0	0
Diarrhea	1	11.8	0	1.7	0	0
	2	7.8	0	0	0	0
	3	20.0	0	0	0	0
Liver dysfunction	1	28.8	6.8	3.4	0	0
	2	17.3	3.8	0	0	0
	3	10.0	0	0	0	0
Renal dysfunction	1	11.9	3.4	0	0	0
	2	3.8	3.8	0	0	0
	3	10.0	0	0	0	0

Number of patients: 59 in the first course, 52 in the second and 10 in the third. Chemo. X: chemotherapy. Liver dysfunction was evaluated by serum aspirate aminotransferase and alamine aminotransferase, and renal dysfunction by serum creatinine.

Renal dysfunction was relatively less frequent and was transient in most patients. However, 2 patients cancelled the second course of chemotherapy due to grade 2 events of serum creatinine.

There were 2 episodes (1.7%) of sepsis during chemotherapy. A 65-year-old woman who had an ileal neobladder-vaginal fistula developed sepsis that originated from urinary tract infection without leukocytopenia and/or neutropenia. The clinical course of the other patient was described above.

There were 2 patients who developed transient grade 1 or 2 peripheral neuropathy. No patients had adverse cardiac events in this study.

DISCUSSION

MVAC chemotherapy is used most frequently in the treatment of patients with metastatic or locally advanced urothelial carcinoma. This combination chemotherapy provides acceptable response rates and longer survival[1]. MVAC may be used often because recent reports suggested that neoadjuvant MVAC is associated with improved survival among patients with locally advanced bladder cancer[6–8]. However, this chemotherapy is associated with various toxicities with a toxic death rate of 3% to 4%[2,3,10,11]. Thus, a similarly efficacious and less toxic chemotherapy regimen should be developed. Von der Maase et al.[2] reported that a combination of gemcitabine and cisplatin (GC) was less toxic than MVAC and had similar efficacy. Although GC may be a less toxic regimen, MVAC is still the standard regimen for treatment of patients with advanced urothelial carcinoma. Thus, adverse events of MVAC should once again be evaluated in the current situation with the various types of supportive care available.

With the development of supportive care, G-CSF and 5-HT_3R antagonists are routinely used for management of adverse neutropenic and gastrointestinal events caused by MVAC. Nevertheless, there have been no reports on how well adverse events with MVAC are managed with the current routine care.

Many reports have revealed that neutropenia (leukocytopenia) is the most frequent and severe adverse event of MVAC[2–6]. This event may cause a serious infection that can lead to toxic death. In this study, grade 3 or 4 neutropenia was seen in about 67.8% of

patients. This number was similar to that in previous reports[2,3] . However, the frequency of febrile neutropenia (5.0%) was lower than that of other studies[2,3]. This difference may stem from the different definition of febrile neutropenia, which is defined as a neutrophil count $<1,000$ and fever $\geq 38.5^{\circ}C$ in the CTCAE and as a neutrophil count <500 and fever $\geq 38.0^{\circ}C$ in the WHO scale. Another possible explanation of the difference may depend on the use of G-CSF. Stenberg et al.[10] reported in their comparative study of high-dose MVAC with classical MVAC that leukocytopenic and neutropenic fevers were significantly less frequent in the high-dose MVAC arm than in the MVAC arm because G-CSF was given to 19% of patients on the MVAC arm, as opposed to 94% on the high-dose MVAC arm. Although most patients recovered safely from neutropenia by using G-CSF without any serious consequence in our study, we should be careful about the development of an unfavorable event as occurred in one patient of the study. Since the current study found that renal function was significantly associated with grade 3 or 4 leukocytopenia and/or neutropenia, MVAC chemotherapy should be prudently indicated for patients having the factor.

Chemotherapy-induced nausea and vomiting can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy treatment. Cisplatin has a very strong nauseant effect and the regimen including this drug is classified as high risk for nausea and vomiting. Prevention of nausea and vomiting is crucial for patients who should continue to receive MVAC. In this study more than one-third of the patients experienced some grade of nausea and vomiting. Nausea of grade 3 or 4 was seen in 17.4% of the patients in the first course and the events led 2 patients to cancel the second course of MVAC. Other reports showed similar frequencies of severe nausea, but it is unclear whether their patients received 5-HT_3R antagonists routinely[2–4,6]. The administration of a 5-HT_3R antagonist with corticosteroids is highly effective and recommended for acute emesis[12,13]. However, it is difficult to control nausea and vomiting completely with these drugs. We hope that a new drug, such as the fifth 5-HT_3 R antagonist and a protachykinin-1 receptor antagonist, will be available soon for prevention of these adverse events[13].

One of the limitations of this study is the small number of patients who received 3 or more courses of the chemotherapy. The frequencies of our febrile neutropenia and sepsis were lower than those of another report, in which patients received a median of four courses[2]. An increase in the number of chemotherapy courses may be potentially associated with the development of severe toxicities. However, there are few reports that discuss whether the grade and frequency of toxicity caused by MVAC are intensified by an increase in the number of chemotherapy courses. There was no significant difference in the frequency and severity of adverse hematological events between the first and the second courses of MVAC in our study. However, since several patients cancelled the second course due to the adverse events, our results may have been biased. Or, rather, the results may indicate that candidates for the second course of MVAC were properly selected, so that the frequency and severity of the events were not enhanced. It may not be possible to extrapolate the current results to all patients who need MVAC chemotherapy. However, patients who receive 2 courses of chemotherapy in the neoadjuvant or adjuvant setting may benefit from the information obtained from this study.

CONCLUSION

We assessed adverse events of MVAC chemotherapy in recent years. MVAC for advanced urothelial cancer has been performed with tolerable adverse events. Although severe neutropenia occurred frequently, similar to previous reports, most patients recovered without life-threatening complications. The use of G-CSF may have contributed to this favorable outcome. The frequency of severe leucopenia/neutropenia was significantly higher in patients with impaired renal function. The current results provide relevant information mainly for those who need 2 courses of chemotherapy in the neoadjuvant or adjuvant setting, although it may not be possible to extrapolate them to patients who need 3 or more courses.

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和文抄録

進行性膀胱尿路上皮癌に対する MVAC 療法の副作用に関する検討

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MVAC 療法の副作用について，G-CSF，5-HT_3 受容体拮抗剤使用下での報告は多くない．今回，われわれは MVAC 療法の副作用について検討した．

1992年 1 月から2004年 9 月までに札幌医科大学附属病院にて MVAC 療法を施行した進行性膀胱尿路上皮癌59例について検討した．副作用の評価は有害事象共通用語基準 v3.0 日本語訳に従って行った．

59人中31例（52.6％）が MVAC を neoadjuvant 療法として受けていた．Neoadjuvant 療法，adjuvant 療法，転移または局所再発に対する治療として 2 コースが最も多く施行されていた．それぞれのコースにおいて，90％以上の症例で白血球減少，好中球減少などの血液毒性が認められた．Grade 3 または 4 の好中球減少は60～75％に認められた．1 コース目における Grade 3 または 4 の白血球減少，好中球減少に関しては，腎機能障害で有意な関連が認められた．発熱性好中球減少は 6 例（5.0％）に認められ，そのうちの 1 例が敗血症性ショック，成人呼吸促迫症候群にて死亡した．非血液毒性としては，嘔気が70～80％に認められた．

進行性膀胱尿路上皮癌に対する MVAC 療法の副作用は許容できる範囲であった．今回の結果は，特に，neoadjuvant 療法，adjuvant 療法として 2 コースを行う際に有用な情報であると思われた．

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